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HER-2 Signaling in Human Breast Cancer

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1. Introduction

1.1 *erb*B family

HER-2 is a member of the *erb*B family of receptor tyrosine kinases. Epidermal Growth Factor Receptor (EGFR) was first identified as the cellular homolog of the transduced oncogene of the avian retroviruses such as avian ERythroBlastosis virus, which causes erythroleukemia and fibrosarcoma and gives rise to the family name (erbB). EGFR, as its name implies, was shown by Stanley Cohen to induce the growth of epidermal cells (Todaro, DeLarco et al. 1976). The EGFR family consists of four members: *erb*B-1 (EGFR), *erb*B-2 (HER-2/neu), *erb*B-3 (HER-3), and *erb*B-4 (HER-4). Her-1, -2, and -3 have been associated with tumorigenesis (Suo, Emilsen et al. 1998). HER-4 has been implicated in development and tumor suppression, possibly by sequestration of the other *erb*B receptors in dimers. Ligand binding stabilizes dimer formation, leading to intracellular signaling. Each receptor consists of an extracellular domain that contains the ligand binding sites, an intracellular domain that contains the tyrosine kinase activity, and a cytoplasmic tail that is involved in cellular signaling. EGFR can be stimulated by an array of ligands, including EGF, transforming growth factor α (TGF-α), heparin-binding EGF (HB-EGF), and heregulins. HER-3 can bind heregulins (Holmes, Sliwkowski et al. 1992); although, it in and of itself does not have an active kinase domain. Heregulin binding to HER-3 facilitates dimerization with other *erb*B receptors which promote the phosphorylation of HER-3 and subsequent activation of downstream signals.

HER-2 does not have any known ligands; however, several intriguing papers have been published recently on this topic. The Calloway group has had a series of papers (Carraway, Carvajal et al. 1993; Carraway and Cantley 1994; Carraway, Sliwkowski et al. 1994; Carraway, Rossi et al. 1999; Komatsu, Jepson et al. 2001; Carraway and Carraway 2007; Kozloski, Carraway et al. 2010) showing that the extracellular domain of HER-2 can bind the intramembrane protein MUC4, suggesting that MUC4 was the ligand for HER-2. MUC4 appears to play a role in mammary gland development at the lactation step along with HER-2. In cancer, MUC 4 blocks apoptosis and stabilizes HER-2/HER-3 dimers. In normal epithelia, MUC 4 sequesters HER-2 to the apical surface, separating it from HER-3, which is on the lateral surface (Carraway and Carraway 2007). These data make a compelling argument for MUC4 as a ligand for HER-2.

More recently, Day, *et al*. (Najy, Day et al. 2008) showed that the extracellular domain of E-cadherin could activate HER-2 and EGFR. They have shown that the extracellular domain of E-cadherin is cleaved by the ADAM proteases. Since E-cadherin is normally present on

epithelial cells and itself, or its sister protein N-cadherin, is present on cancer cells of epithelial origin, it is also a good candidate for a HER-2 ligand.

Pairings of the *erb*B receptors have been exquisitely elucidated by Josef Yarden and colleagues (Goldman, Benlevy et al. 1990; Karunagaran, Tzahar et al. 1996; Alroy and Yarden 1997). Yarden, *et al*. utilized the 32D cell line, an IL-3-independent murine myeloid cell line that does not express endogenous *erb*B receptors. They systematically expressed each family member separately and in pairs to determine which family members formed complexes. They found that each family member can homodimerize or heterodimerize with every other family member; although, certain heterodimers are preferred. Which dimer is present on the cell determines the biological phenotype of that cell. Although EGFR can homodimerize, it will pair with HER-2 when HER-2 is present and will only pair with itself when all of the HER-2 is paired or no HER-2 is present (Hendriks , Opresko et al. 2003).

EGFR dimerization results in the phosphorylation of tyrosine 1045 in the cytoplasmic domain. Phosphorylation of this tyrosine creates a docking site for the *cbl* protein (Yokouchi, Kondo et al. 1999). *Cbl* then recruits ubiquitin which targets the EGFR for degradation (Yokouchi, Kondo et al. 1999). Activation of HER-2 does not create a ubinquitin binding site, so HER-2 does not get degraded upon activation unless it is dimerized with EGFR. Over expression of HER-2 results in constitutive activation of both HER-2 and EGFR and in a decrease in degradation of both of the receptors.

Due to the fluidity of the plasma membrane, transient dimerization of the *erb*B receptors occurs. However, the transient dimers do not elicit a strong signal. Our model (*FIGURE 1*) (Woods Ignatoski, LaPointe et al. 1999) suggests that over expression of HER-2 leads to many transient homodimers. The transient homodimers lead to transphosphorylation of the receptor causing many small signals to be initiated. The overall effect is one of a strong, ligand-stabilized signal which results in constitutive activation of HER-2 and constitutive growth signals (*FIGURE 1C*). The type of HER-2 homo and heterodimerization, coupled with over expression, on mammary epithelial cells has consequences dealing with normal development, proliferation, and transformation.

2. HER-2 in development

HER-2 is expressed in almost all fetal tissues including the placenta, liver, kidney, mammary gland, brain, and lung (Kokai, Wada et al. 1988). On the basis of its expression pattern, HER-2 plays a role in general development. Although HER-2's role in tumorigenesis has been studied extensively, its role in normal mammary gland development has not. There are many articles about mammary gland development in HER-2 transgenic and knock-out mice, but since human and mouse mammary glands develop differently, the actual role of HER-2 in human mammary gland development is not fully understood. Mina Bissell and colleagues developed the three-dimensional *Matrigel* system to study mammary gland morphogenesis, discovering the role for integrins in anti-apoptotic signaling (Petersen, Ronnovjessen et al. 1992; Howlett, Bailey et al. 1995; Lochter, Galosy et al. 1997; Lochter, Navre et al. 1999). Joan Brugge and colleagues refined the *Matrigel* model to identify HER-2 as a modulator of the lumen compartment, by working through Bim-1 to regulate apoptosis of the pre-lumenal cells (Muthuswamy, Li et al. 2001). One caveat to the Brugge group's work is the use of a chimeric molecule that has an NGF extracellular domain and a HER-2 cytoplasmic domain that can be crosslinked to give a constitutive signal. While their work leads to important insight into the role of HER-2 in development, the system they use is not

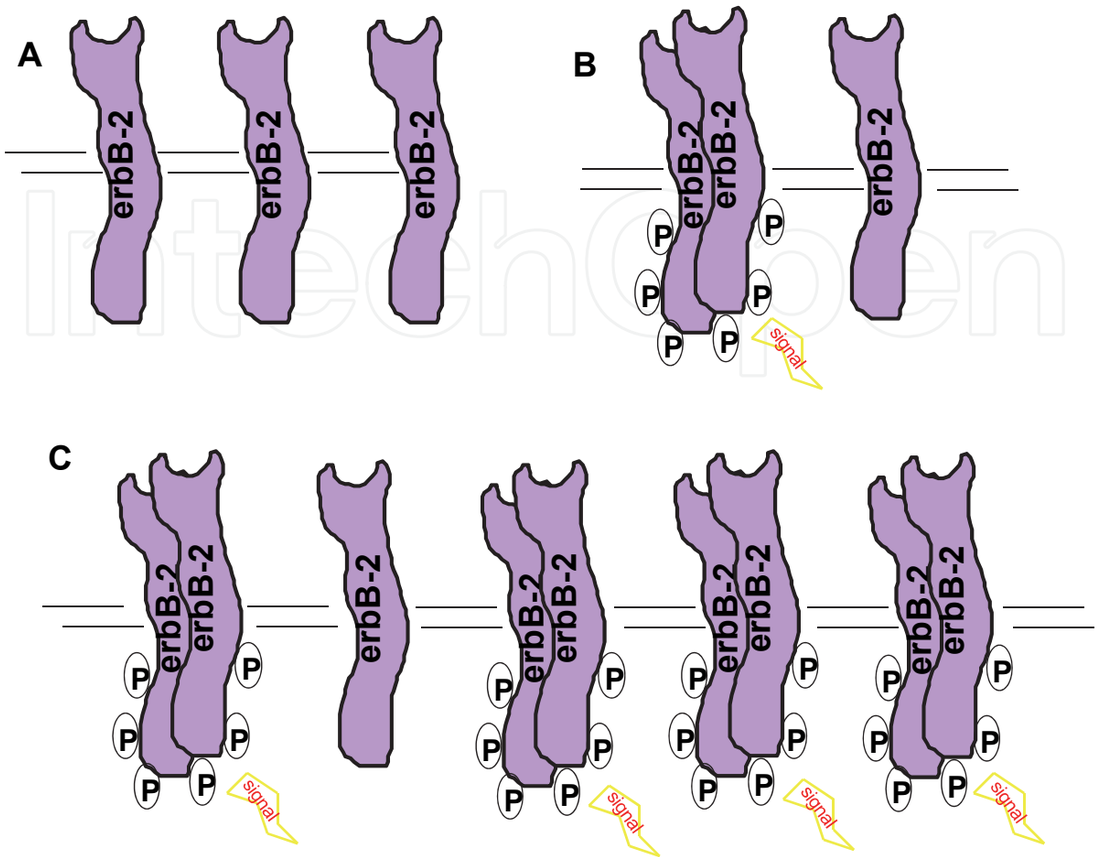

Fig. 1. Schematic of signaling from HER-2 during normal conditions and during over expression. (A) HER-2 is normally present as single molecules in the plasma membrane. (B) Due to the fluid nature of the membrane, random, transient dimers form producing weak signals that cannot elicit a response from the cell. (C) During over expression, many transient dimers produce a signal strong enough to elicit a response from the cell.

physiological, since HER-2 is not activated by a ligand but rather by the amount of protein, and constitutive HER-2 activation is not done by cross-linking the cytoplasmic domains. Recently, we have developed a system that is more physiological than the one used by Brugge and colleagues (manuscript submitted). We used human mammary epithelial (HME) cells, obtained from reduction mammoplasties, plated in *Matrigel* to study the role of HER-2 in branching morphogenesis. We observed that HME cells form branching structures when plated in the 3D matrix *Matrigel* and determined that HER-2 is up-regulated at the time of branching. Using HER-2 over expressing HME cells (Woods Ignatoski, LaPointe et al. 1999) we showed that constitutive activation of HER-2 was necessary and sufficient to form the branches. By using genetic and chemical activators and inhibitors, we showed that AKT activation mediated the HER-2-facilitated branching morphogenesis. Our data imply that HER-2's role in mammary gland development is to facilitate ductal formation.
Korkaya, *et al*. (Korkaya, Paulson et al. 2008) and Magnifico, *et al*. (Magnifico, Albano et al. 2009) have shown that an increase in HER-2 in human mammary stem cells causes an increase in mammosphere formation and an increase in ductal structures when the cells are

placed in animals. Both groups have also shown a reciprocal relationship between over expression of HER-2 and the expression of the developmental gene Notch. Their published data suggest that HER-2-mediated AKT activation is necessary for self-renewal leading to the ductal structures in their mouse models. Our data show that HER-2-mediated AKT activation is necessary for branching morphogenesis and is concordant with the data presented by Korkaya, *et al*. (Korkaya, Paulson et al. 2008) and Magnifico, *et al*. (Magnifico, Albano et al. 2009).

Since we have previously shown that HME cells in *Matrigel* and HER-2 over expressing cells have an increase in Focal Adhesion Kinase (FAK) phosphorylation (Woods Ignatoski and Ethier 1999), an implication of these data is that signaling from integrin binding to extracellular matrix may also play a role in this developmental phenotype. Indeed, Bissell, *et al*. (Petersen, Ronnovjessen et al. 1992; Howlett, Petersen et al. 1994; Howlett, Bailey et al. 1995; Gudjonsson, Ronnov-Jessen et al. 2002), has shown that β1 integrin is important in mammary cell morphology change. β1 integrins bind to and activate FAK (Zachary and Rozengurt 1992). FAK was shown to maintain the mammary gland stem cell pool (Nagy, Wei et al. 2007). Since HER-2 has recently been shown to play a role in human mammary stem cells (Korkaya, Paulson et al. 2008; Korkaya and Wicha 2009), the idea that FAK may be downstream of HER-2 to maintain the stem cell population is intriguing.

3. HER-2 signaling in transformation

HER-2 uses a variety of signaling pathways to elicit phenotypes associated with transformation and tumorigenesis. We and others used various *in vitro* methods in conjunction with constitutively active and dominantly negative mutants and chemical inhibitors to elucidate the multiple pathways HER-2 uses to transform cells (*FIGURE* 2).

Growth factor independence: One hallmark of a transformed cell is growth factor independence. Ram, *et al*. (Ram, Kokeny et al. 1995; Ram, Dilts et al. 1996) showed that human breast cancer (HBC) cells with increasing amounts of HER-2 had increasing degrees of growth factor independence. H16N2 cells, which are non-transformed, immortalized HME, have normal levels of HER-2 and required both insulin-like growth factor (IGF) and epidermal growth factor (EGF) to survive. 21MT-2 cells with an slight over expression of HER-2 still required EGF, but 21MT-1 cells with a clinically relevant HER-2 over expression did not require either IGF or EGF for growth. To determine the contribution of HER-2 over expression to growth factor independence without the other genetic abnormalities associated with HBC, we developed HME cell lines that over expressed HER-2 less than the HPV16-immortalized HME cell line (H16N2).

The MCF-10HER-2 cells were unable to grow in the absence of IGF, showing that a slight over expression resulted in IGF independence and that over expression to levels seen in amplified HBC cells conferred both IGF and EGF independence to the H16N2 cells (Woods Ignatoski, LaPointe et al. 1999). Over expression of HER-2 resulted in progressively increasing levels of tyrosine-phosphorylated HER-3, without any significant changes in HER-3 protein levels (Woods Ignatoski, LaPointe et al. 1999).

Our studies, while demonstrating a direct relationship between the level of expression, the activation of HER-2, and the requirements for IGF and EGF, suggest that genetic alterations present in breast cancer cells, or mediated by HPV-16-induced alterations, can influence the expression level and activation status of HER-2 and, in turn, their degree of growth factor independence. To this end, we were intrigued by the differences between

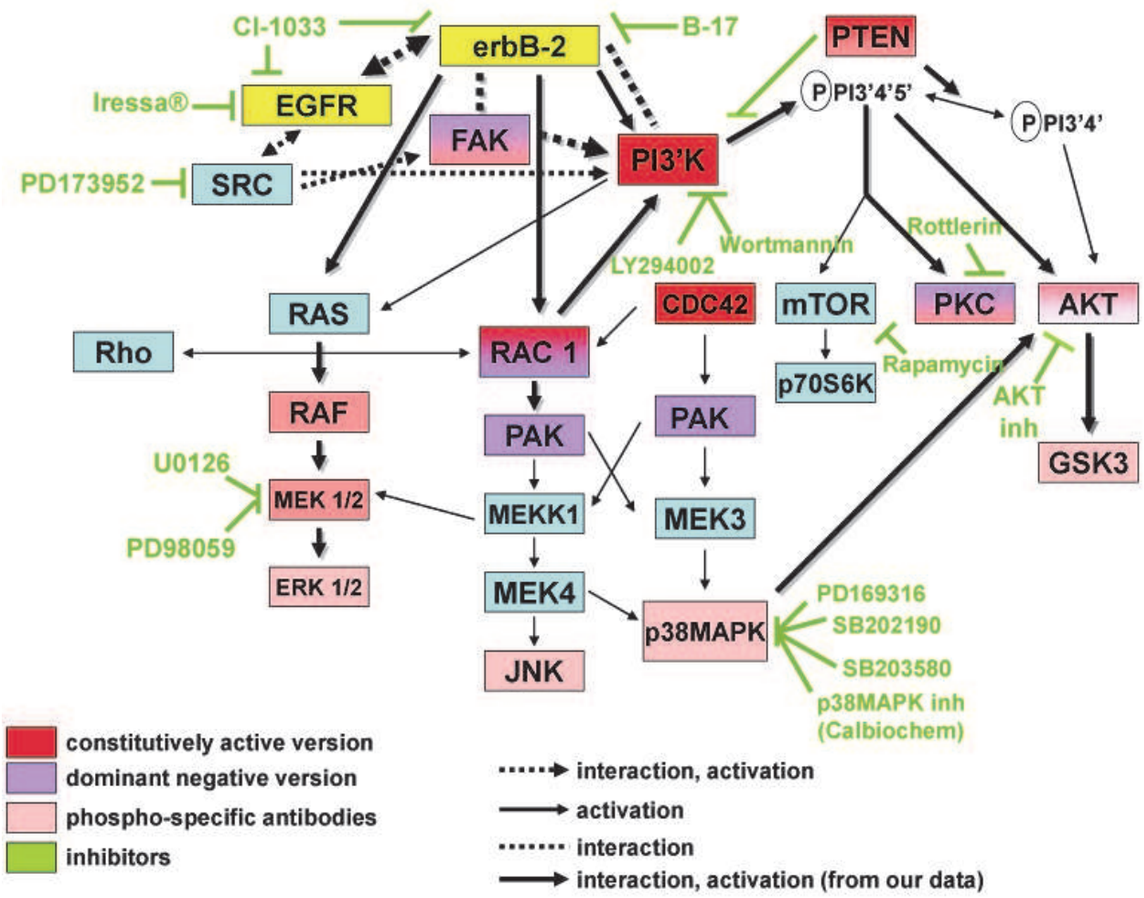

Fig. 2. The tools used to decipher HER-2 signaling. Various constitutively active and dominant negative constructs plus specific chemical inhibitors and phospho-specific antibodies were used to elucidate downstream signaling for HER-2 and associate them with transformed phenotypes.

the MCF-10A cell line and the H16N2 cell line in terms of their ability to over express HER-2 and their differences in growth factor independence. The biggest difference in the parental cell lines is the inclusion of the entire HPV16 genome in the H16N2 cells which is not in the MCF-10A cells. The HPV-16 genome produces the HPV E5, E6, and E7 oncogenes which have been shown to affect the tumor suppressors Rb and p53, among other proteins. To discern if the HPV genes played a role in HER-2-mediated transformation, we co-expressed E6, E7, or E6 and E7 with HER-2 in MCF-10A cells and tested for transformed phenotypes (Woods Ignatoski, Dziubinski et al. 2005). Co-expression of HER-2 with the HPV-16 oncoproteins E6 and E7 resulted in the emergence of fully EGF-independent cells that expressed very high levels of constitutively activated HER-2. Interestingly, co-expression of E7 with HER-2 resulted in cells that were EGF-independent for growth but which did not express HER-2 to higher levels than control MCF-10HER-2 cells. By contrast, co-expression of E6 with HER-2 resulted in cells expressing higher levels of HER-2 but which were still dependent on EGF for growth and survival. Examination of the expression and activation status of HER-1, -2 and -3 in the MCF-10HER-2 cells and their derivatives by

immunoprecipitation/western blot analysis demonstrated that the EGF-independent MCF-10HER-2E7 cells and the HER-2/E6E7 cells exhibited constitutive EGF-independent activation of EGFR. Further, the constitutively active EGFR had a faster electrophoretic mobility than EGFR activated by exogenous growth factors. Exposure of MCF-10HER-2 cells and their derivatives as well as the HER-2 amplified SUM-225 breast cancer cell line to ZD1839 (IRESSA®) at concentrations specific for EGFR, eliminated EGFR tyrosine phosphorylation, blocked proliferation, but only modestly altered the levels of constitutively activated HER-2. By contrast, exposure of SUM-190 cells or MDA-351 cells, which have amplified HER-2 but express little or no EGFR, to these same concentrations of ZD1839 had little or no influence on cell proliferation. Our results showed that HER-2 over expression cooperates with EGFR and HPV-E7 to yield HME cells that are EGF-independent for growth. Together, HER-2, E6 and E7 cooperate with endogenous EGFR to yield fully transformed cells that express very high levels of HER-2 and that are growth factor autonomous for proliferation and survival.

Phophotidylinositol 3′ kinase (PI3′K) phosphorylates inositol in the plasma membrane at the 3′ position. Phosphorylation of inositol produces a docking site for the serine/threonine kinase AKT. Docking of AKT activates its kinase activity and elicits downstream signals. Activation of both HER-2 and HER-3 provide phosphotyrosines that can dock PI3′K and bring it to the membrane; therefore, activation of HER-2 mediates inositol phosphorylation and PI3′K signaling (Fedi, Pierce et al. 1994). Phospho-AKT remained detectable in HER-2 cells treated with the PI3′K inhibitor LY294002 or with expression of exogenous PTEN, a phosphatase that reverses the action of PI3′K, but was abolished by treatment with the p38 mitogen activated kinase (p38MAPK) inhibitor SB202190. Thus, both PI3K-dependent and p38MAPK-dependent pathways lead to activation of AKT. We also found that AKT was activated by p38MAPK in these cells, but this activation did not play a role in invasion (Woods Ignatoski, Livant et al. 2003). Since AKT has been shown in other systems to be a survival factor (Datta, Dudek et al. 1997; Brunet, Bonni et al. 1999; Hutchinson J, Jin J et al. 2001), we hypothesized that HER-2 mediated activation of AKT is necessary for growth factor independence. We found that, in the absence of EGF, p38MAPK-activated AKT is necessary for HER-2 over expressing cells to survive and to form colonies in soft agar (Woods Ignatoski, Livant et al. 2003). We showed that EGF works as a survival signal in the absence of p38MAPK-mediated activation of AKT and that HME cells expressing a constitutively active AKT did not require EGF for growth or colony formation in soft agar. Thus, our data indicate that AKT activation can compensate for EGF-mediated cell survival signals leading to growth factor-independence and anchorage-independent growth (Diehl, Grewal et al. 2007).

HER-2 in invasion: Using a model system for invasion that utilizes a naturally occurring membrane found in sea urchin embryos (Livant, Linn et al. 1995) in the configuration a cell would see upon extravasation (*FIGURE 3*), we determined that α5 integrin binding to the PHSRN sequence of fibronectin is necessary for invasion and that α4 integrin binding to the "LDV" sequence of fibronection abrogates invasion (Livant, Allen et al. 2000; Livant, Brabec et al. 2000; Woods Ignatoski, Maehama et al. 2000; Jia, Markwart et al. 2002) (*FIGURE 4*). Using this system, we showed that HER-2 requires PI3′K to drive invasion. With this same system we also showed that HER-2 mediates the down-regulation of α4 integrin from the cell surface to facilitate invasion via activation of p38MAPK (Woods Ignatoski, Maehama et al. 2000) (FIGURE *5*).

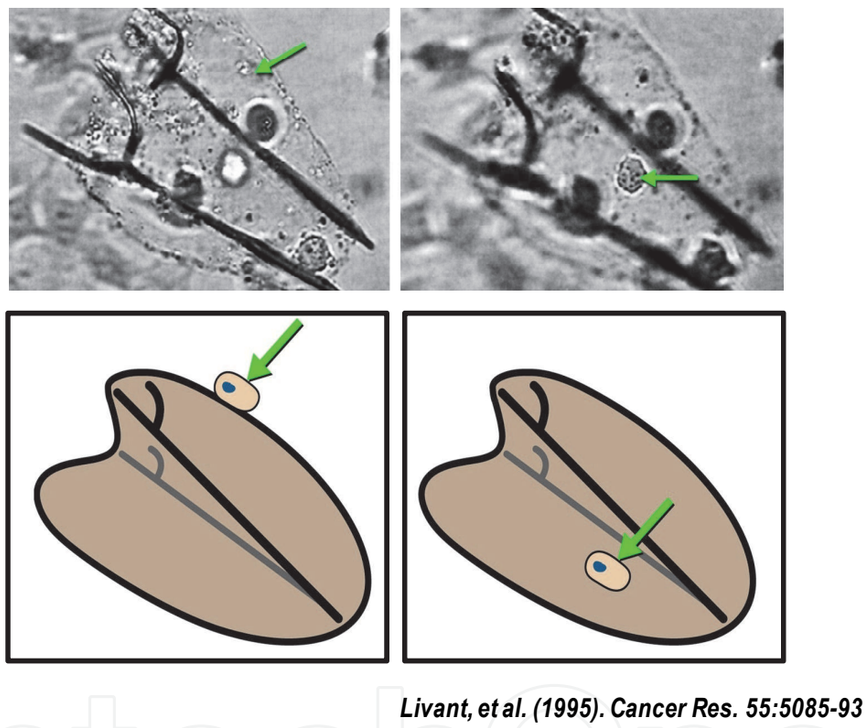

Fig. 3. Sea urchin embryo invasion assay. This assay utilizes the naturally occurring membrane found under a cell layer in sea urchin embryos. The outer cell layer is lysed and the cells are placed on top of the embryos. The number of cells that enter the embryo are blindly scored. Arrows point to cancer cells.

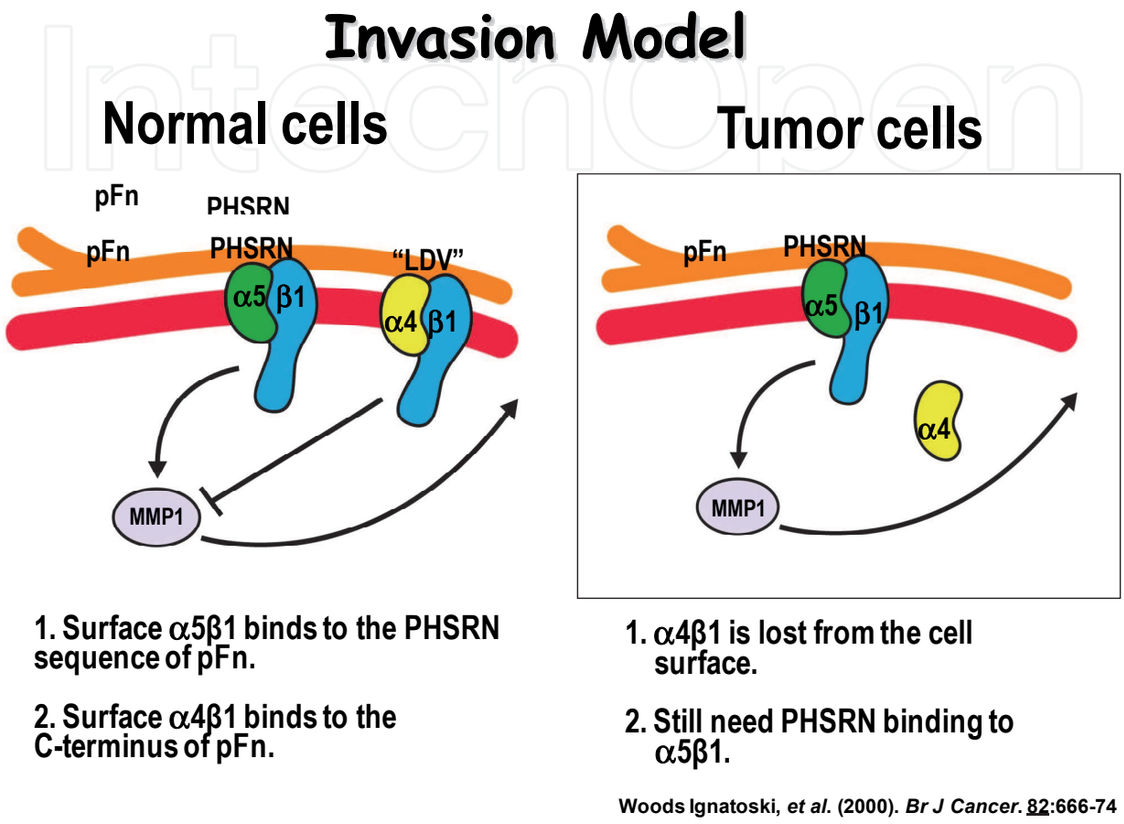

Fig. 4. Model of how cells are able to invade basement membranes. Fibronectin can bind α5 integrin through the PHSRN sequence. This binding drives the expression of MMP-1 and facilitates invasion. However, on normal cells, fibronectin binding to α4 integrin blocks MMP-1 release. On cancer cells, α4 integrin is not present on the cell surface, so invasion can proceed.

Utilizing a constitutively active form of PI3K, p110CAAX, we showed that PI3K can mediate most phenotypes observed in HER-2-overexpressing cells. PTEN expression blocked HER-2-mediated invasion. Down-regulated α4 integrin sequestered PTEN away from the surface, allowing PI3'K to activate PKCδ and facilitate the release of MMP-1 to drive invasion. These results led us to a model for HER-2-mediated invasion where the down-regulation of α4 integrin works in concert with the activation of PI3'K to facilitate the release of MMP-1 and drive invasion (*FIGURE 5*).

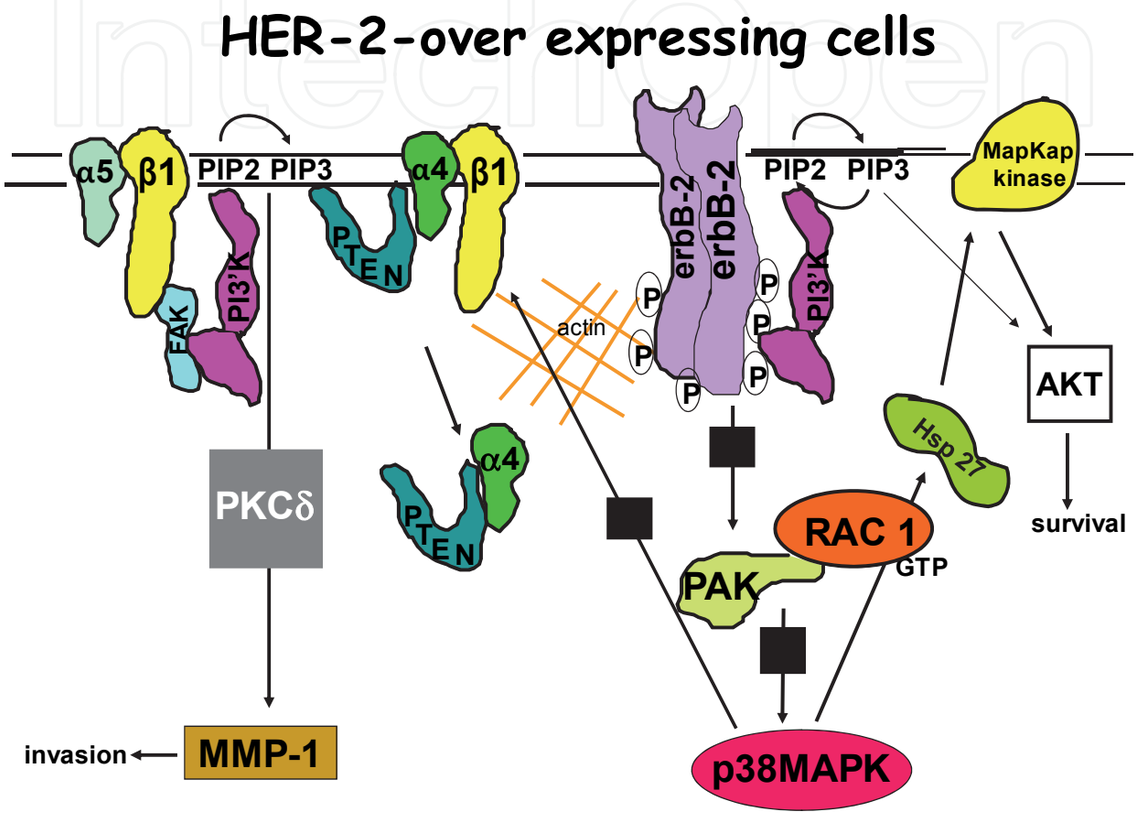

Fig. 5. Schematic of the signal pathways mediated by HER-2. HER-2 activates Rac 1 which activates p38MAPK. P38MAPK rearranges the actin cytoskeleton drawing α4 from the cell surface. It is hypothesized that PTEN is sequestered in the cytoplasm via its association with α4 (data not shown). Sequestration of PTEN allows PI3'K to activate PKCδ to release MMP-1 and facilitate invasion. P38MAPK also activates Hsp27 which activates MapKap kinase and, subsequently, AKT. AKT then facilitaes EGF-independent survival.

Using other *in vitro* transformation methods including anchorage-independent growth and cell motility assays, we were able to show that the PI3'K pathway can mediate most phenotypes observed when HER-2 is over expressed (Woods Ignatoski, Livant et al. 2003; Diehl, Woods Ignatoski et al. 2004). The HER-2-mediated signaling pathways are summarized in *FIGURE 6*.

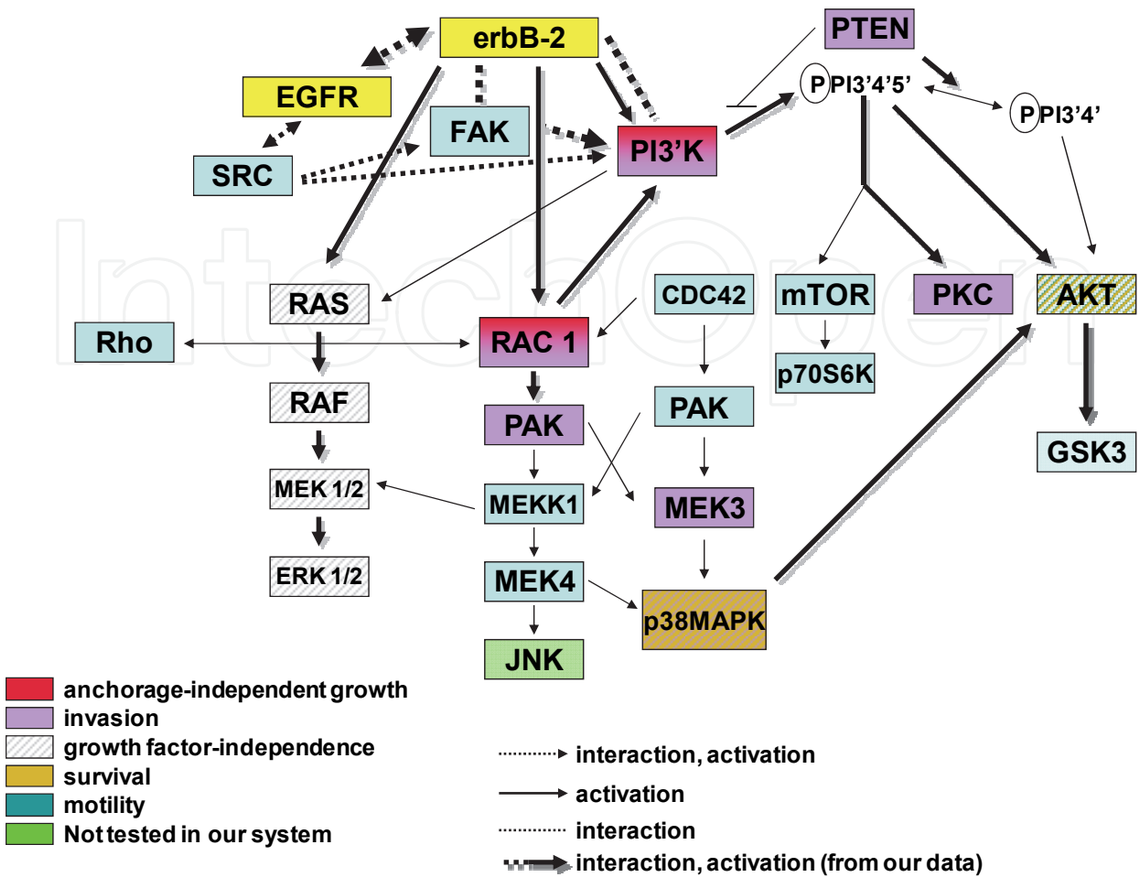

Fig. 6. Diagram of the HER-2-mediated signaling and designation of which pathways facilitate which transformed phenotypes.

Anti-HER-2 therapeutics: The presence of HER-2 over expression in HBC confers a poor prognosis (Slamon, Clark et al. 1987). Thus, the ultimate goal of the study of HER-2 is to offer women with HER-2 over expressing breast cancer an effective therapy. To this end, two relatively effective anti-HER-2 therapies have been FDA approved: trastuzumab (Herceptin®, *Genentech*) and lapatinib (Tykerb®, *Glaxo Smith-Kline*). Trastuzumab is a humanized anti-HER-2 antibody (Ewer, Gibbs et al. 1999; Palmieri, Powles et al. 2001; Rudlowski, Rath et al. 2001). The exact mode of action for trastuzumab is not known; however, trastuzumab is effective against 12-26% of HER-2-positive metastatic patients. Much of the resistance to trastuzumab has been shown to involve over activation of the PI3'K/ AKT pathway (O'Brien, Browne et al. 2010; Migliaccio I, Gutierrez et al. 2011). The survival advantage conferred upon a cell with an activated AKT overcomes the loss of HER-2 activity. Recently, Miller, *et al.* (Miller , Forbes et al. 2009) showed that trastuzumab in combination with rapamycin, which blocks the AKT pathway downstream of AKT at mTOR, could block HER-2 positive tumor growth in mice better than either treatment alone. Also, Zhang, *et al.* (Zhang, Huang et al. 2011) has shown that trastuzumab in combination with the *Src* inhibitor saracatinib can decrease HER-2 positive tumor growth in animals. *Src* is a non-receptor tyrosine kinase that has been shown to play a role in tumorigenesis. Zhang, *et al.* go on to show that *Src* activation is necessary for trastuzumab resistance and

that all of the pathways that cause trastuzumab resistance, including different pathways that over activate AKT, originate from over active *Src*. Combination therapies, as the ones above, will be useful when using trastuzumab against HER-2 positive breast cancer.

Glaxo Smith-Kline has developed a small molecule EGFR/HER-2 dual inhibitor called lapatinib (Konecny, Pegram et al. 2006; Rusnak, Alligood et al. 2007; Molina, Kaufmann et al. 2008). Lapatinib has been shown to be a potent HER-2 inhibitor and a useful therapeutic against HER-2 positive breast cancer. Lapatinib, a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domain of HER-2, is used with capecitabine for the treatment of advanced HER2-positive metastatic breast cancer (Molina, Kaufmann et al. 2008). Since response to lapatinib is predicted specifically by low levels of PTEN (Migliaccio I, Gutierrez et al. 2011) and resistance to trastuzumab is dependent on activation of the PI3'K pathway, studies showing the efficacy of a dual therapy using both lapatinib and trastuzumab will be very useful.

4. Conclusions

HER-2-mediated signaling is a convergence point that controls ductal development, the activity of the EGFR family of receptors, and many transformed phenotypes. Significantly abrogating the function of HER-2 is necessary to achieve prolonged survival for breast cancer patients.

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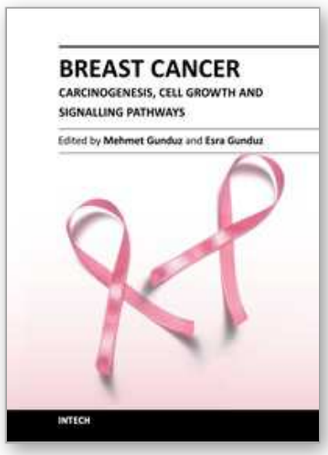

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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